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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: COMBINATION THERAPY FOR CONDITIONS LEADING TO BONE LOSS

(57) Abstract: The present invention discloses a novel secreted polypeptide, termed osteoprotegerin, which is a member of the tumor necrosis factor receptor superfamily and is involved in the regulation of bone metabolism. Also disclosed are nucleic acids encoding osteoprotegerin, polypeptides, recombinant vectors and host cells for expression, antibodies which bind OPG, and pharmaceutical compositions. The polypeptides are used to treat bone diseases characterized by increased resorption such as osteoporosis. Methods of treatment are described using the polypeptides in conjunction with various agents, including IL-1 inhibitors, TNF- α inhibitors, and serine protease inhibitors.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/18667

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/17 A61K38/20 A61K38/55 A61K47/48 A61P19/00
 A61P25/00 A61P29/00 A61P37/00 //C07K14/705,
 C12N15/12, (A61K38/17,38:20), (A61K38/17,38:55), (A61K38/17,38:20,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE, SCISEARCH, EMBASE, CANCERLIT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 784 093 A (AMGEN INC) 16 July 1997 (1997-07-16) cited in the application abstract page 12, line 41 - line 49; claims 1-60 ---	1,2, 6-13, 17-25, 30-42
A	ROODMAN G D: "ROLE OF CYTOKINES IN THE REGULATION OF BONE RESORPTION" CALCIFIED TISSUE INTERNATIONAL, NEW YORK, NY, US, vol. 53, no. SUPPL. 01, 1993, pages S94-S98, XP000940463 ISSN: 0171-967X page S95, left-hand column, paragraph 3 -right-hand column, paragraph 1 --- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"G" document member of the same patent family

Date of the actual completion of the international search

24 January 2001

Date of mailing of the international search report

12 07. 2001

Name and mailing address of the ISA

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NIEMANN, F

INTERNATIONAL SEARCH REPORT

International Application No

PC, /US 00/18667

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 38:55), (A61K38/20, 38:55)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93 21946 A (RUSSELL DEBORAH A ; THOMPSON ROBERT C (US); SYNERGEN INC (US)) 11 November 1993 (1993-11-11) abstract claims 1-15	
A	--- MARTIN T J ET AL: "Interleukins in the control of osteoclast differentiation." CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, (1998) 8 (2) 107-23. REF: 143, XP000979080 the whole document -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/18667

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1,2,6-13,17-25,30-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see further information sheet invention 1.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,39-42 (partially), 6-13,17-25,30-38

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with TNF-alpha inhibitors.

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with TNF-alpha inhibitors and IL-1 inhibitors.

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with TNF-alpha inhibitors and serine protease inhibitors.

2. Claims: 1,2,39-42 (partially) 14-16, 26-29

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with serine protease inhibitors.

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with serine protease inhibitors and IL-1 inhibitors.

3. Claims: 1,2 (partially),3-5

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with serine protease inhibitors.

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with serine protease inhibitors and IL-1 inhibitors.

4. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with IL-6 inhibitors.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with IL-8 inhibitors.

6. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with IL-18 inhibitors.

7. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with ICE modulators.

8. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with FGF-1 to FGF-10, FGF modulators.

9. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with PAF antagonists.

10. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with MMP modulators.

11. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with NOS modulators.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

12. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with modulators of glucocorticoid receptor.

13. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with modulators of glutamate receptor.

14. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with modulators of LPS level.

15. Claims: 1,2 (partially)

a method for treating conditions leading to bone loss, which comprises administering a therapeutically effective amount of a purified and isolated OPG protein in conjunction with noradrenaline or modulators and mimetics thereof.

16. Claims: 43-48

a method of treating an IL-1 mediated disease, wich comprises administering therapeutically effective amounts of an IL-1 inhibitor and a serine protease inhibitor

17. Claims: 49-57

a method of treating an TNF-mediated disease, wich comprises administering therapeutically effective amounts of a TNF-alpha inhibitor and a serine protease inhibitor

18. Claims: 58-61

a method of treating inflammation, rheumatoid arthritis, SLE, GvHD, which comprises administering an IL-18 inhibitor, a TNF-alpha inhibitor, and an IL-1 inhibitor

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/18667

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